



**DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute
National Institute of Environmental Health Sciences**

REPORT TO THE U.S. CONGRESS

THE LONG ISLAND BREAST CANCER STUDY PROJECT

November 2004

**Department of Health and Human Services
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REPORT ON THE LONG ISLAND BREAST CANCER STUDY PROJECT (LIBCSP)

EXECUTIVE SUMMARY

The Long Island Breast Cancer Study Project (LIBCSP) was initiated in 1993 in response to Public Law 103-43, June 10, 1993, and has been funded and coordinated by the National Cancer Institute (NCI), in collaboration with the National Institute of Environmental Health Sciences (NIEHS). The multistudy LIBCSP has been investigating whether environmental factors are responsible for breast cancer in Suffolk, Nassau, and Schoharie Counties, New York, and Tolland County, Connecticut. The LIBCSP is part of overall research efforts of the National Institutes of Health (NIH) to investigate the causes of breast cancer and find ways to prevent the disease.

The law directed that a study be conducted of “potential environmental and other risks contributing to the incidence of breast cancer” in Nassau and Suffolk Counties and the two counties with the highest age-adjusted mortality rates for breast cancer during 1983-1987, which were Schoharie and Tolland Counties. In addition, the law directed that the study “shall include the use of a geographic system to evaluate the current and past exposure of individuals, including direct monitoring and cumulative estimates of exposure, to: (1) contaminated drinking water; (2) sources of indoor and ambient air pollution, including emissions from aircraft; (3) electromagnetic fields; (4) pesticides and other toxic chemicals; (5) hazardous and municipal waste; and (6) such other factors as the [NCI] director determines to be appropriate.”

The LIBCSP consists of human population (epidemiologic) studies, the establishment of a family breast and ovarian cancer registry, and laboratory research on mechanisms of action and susceptibility in the development of breast cancer. Most of the studies were conducted by scientists at major medical research institutions in the Northeastern United States, and most of the results have been reported in peer-reviewed journals. These studies and the Principal Investigators are:

- *Breast Cancer and the Environment on Long Island Study* (centerpiece case-control study) and *Breast Cancer and the Environment on Long Island Follow-up Study* – Marilie D. Gammon, Ph.D., Columbia University, New York, NY, and then the University of North Carolina at Chapel Hill, North Carolina
- *Electromagnetic Fields and Breast Cancer on Long Island Study* – M. Cristina Leske, M.D., M.P.H., Stony Brook University, Stony Brook, New York
- *Epidemiology of Breast Cancer and Serum Organochlorine* and *Serum Organochlorine Compounds and Breast Cancer on Long Island* – Steven D. Stellman, Ph.D., American Health Foundation, Valhalla, New York

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- *Organochlorine Compounds and Risk of Breast Cancer* – Tongzhang Zheng, M.D., Sc.D., Yale University, New Haven, Connecticut
- *Environmental Exposures and Breast Cancer on Long Island* – Erin O’Leary, Ph.D., University of Buffalo, Buffalo, New York
- *Reducing Barriers to Use of Breast Cancer Screening* – Dorothy S. Lane, M.D., M.P.H., Stony Brook University, Stony Brook, New York
- *Estrogen Metabolites as Biomarkers for Breast Cancer Risk* – H. Leon Bradlow, Ph.D., Strang Cancer Prevention Laboratory, New York, New York, and Geoffrey Kabat, Ph.D., Stony Brook University, Stony Brook, New York
- *Regulation of Scatter Factor Expression in Breast Cancer* – Eliot M. Rosen, M.D., Ph.D., Long Island Jewish Medical Center, Albert Einstein College of Medicine, New Hyde Park, New York
- *RDA Analysis of Breast Cancer* – Michael H. Wigler, Ph.D., Cold Spring Harbor Laboratory, Cold Spring Harbor, New York
- *Metropolitan New York Registry* – Ruby T. Senie, Ph.D., M.S., Columbia University, New York, New York

The LIBCSP is an extramural research program; however, several studies were conducted by NCI scientists:

- *New Statistical Methodology for Determining Cancer Clusters* – Martin Kulldorff, Ph.D., now at the University of Connecticut Health Center, Farmington, Connecticut
- *Geographic Influences on Women’s Health* – Susan R. Sturgeon, Dr.P.H., now at the University of Massachusetts, Amherst, Massachusetts
- *New York State Cancer Registration Project* – Brenda Edwards, Ph.D., NCI, Bethesda, Maryland

The LIBCSP also included development of a new research tool, the Geographic Information System for Breast Cancer Studies on Long Island (LI GIS), for researchers to use to investigate relationships between breast cancer and the environment and to estimate exposures to environmental contamination. Geographic information systems (GIS) are powerful computer systems that permit layers of dissimilar information (e.g., geographic, demographic, environmental, and breast cancer data) to be superimposed and analyzed.

Findings on the primary hypotheses have been reported from most of the LIBCSP studies. These completed investigations have:

- Demonstrated that organochlorine compounds (e.g., pesticides including DDT/DDE, dieldren, and chlordane, and polychlorinated biphenyls [(PCBs)^a) are not associated with increased risk for breast cancer on Long Island;
- Found that polycyclic aromatic hydrocarbons (PAHs)^b were associated with a modest increased risk for breast cancer, which will need to be confirmed in studies of other populations;
- Found that PCBs may be associated with an increased risk for recurrence of breast cancer, which is being investigated further (numbers were small, and no association had been seen with initial diagnosis of cancer);
- Demonstrated that electromagnetic fields (EMFs)^c are not associated with increased risk for breast cancer on Long Island;
- Confirmed the presence of established risk factors for breast cancer among women on Long Island;
- Supported exploratory research on urinary biomarkers for early detection of breast cancer;
- Demonstrated effective methods to improve breast cancer screening among underusers of mammography;
- Furthered laboratory research on mechanisms of action and susceptibility to breast cancer that have contributed to our understanding of the process of tumor development;
- Developed new and improved research methods to advance epidemiologic investigations;
- Established a breast/ovarian cancer family registry that is a research resource for investigators, provides opportunities for families to participate in research, and now is part of a larger NCI program;
- Developed the LI GIS as a research tool for studying relationships between the environment and breast cancer;

^a PCBs are a group of organochlorine compounds used widely in coolants and lubricants.

^b PAHs are pollutants caused by incomplete combustion of various chemicals, such as diesel fuel and cigarette smoke.

^c EMFs are electric and magnetic fields produced by the generation, transmission, and use of electric energy.

- Funded pilot studies on the use of LI GIS in research on breast cancer and the environment;
- Provided the basis for spinoff studies using data and biospecimens from the centerpiece case-control study for investigations on genetic susceptibility and the potential role of gene-environment interactions in breast cancer causation. These studies are conducted independent of the LIBCSP with support from various research funding organizations; and
- Data were collected for Tolland and Schoharie Counties, although valid analyses could not be conducted because the number of women with breast cancer was too few in each location.

The findings from the LIBCSP may offer reassurance to concerned individuals. Nevertheless, LIBCSP investigators continue to conduct additional analyses. Dr. Gammon's Breast Cancer and the Environment on Long Island Follow-up Study follows women with breast cancer who participated in her initial case-control study to determine whether certain chemical exposures influence breast cancer outcomes. Dr. Gammon also continues to conduct additional analyses on data and biospecimens collected in her initial study. Dr. Leske continues to perform additional analyses on data from her EMF study. Dr. Sturgeon continues her research on geographic influences and risk for breast cancer.

The LIBCSP applied the best available science and technologies in pursuit of relationships between the environment and increased risk for breast cancer, and yielded high-quality research. The mandate of the Public Law has been met with the successful conduct of the epidemiologic studies and the development of the LI GIS. Total estimated funding for the LIBCSP is \$30,035,000 for fiscal years (FY) 1993 through 2004.

A new generation of research on breast cancer and the environment is underway. Research may not be ongoing in a specific geographic location, but the overarching aim of epidemiologic research is to generate findings that can be generalized to and benefit the larger population. These new activities include:

- NIEHS, in collaboration with NCI, is funding four new Breast Cancer and the Environment Research Centers (BCERC) to study the prenatal-to-adult environmental exposures that may predispose a woman to breast cancer.
- A transagency task force, initiated by NCI and including NIEHS, Centers for Disease Control and Prevention (CDC), and U.S. Environmental Protection Agency (EPA), is making steady progress on a proposed plan to address breast cancer rates in Marin County, California, and other counties in the United States.
- NIEHS scientists are conducting a prospective study of a cohort of unaffected sisters of women who have had breast cancer. The Sister Study will prospectively examine

environmental and familial risk factors for breast cancer and other diseases in a cohort of 50,000 sisters of women who have had breast cancer. Such sisters have about twice the risk of developing breast cancer as other women.

- NCI has launched an initiative to pool data and biospecimens from 10 large study populations to conduct research on gene-environment interactions in cancer etiology. The investigative teams will collaborate on studies of hormone-related gene variants and environmental factors involved in the development of breast as well as prostate cancer.

NCI and NIEHS remain committed to advancing our understanding of potential relationships between environmental exposures and risk for breast cancer.

Report on the Long Island Breast Cancer Study Project

I. Introduction

The Long Island Breast Cancer Study Project (LIBCSP) was initiated in 1993 in response to Public Law 103-43, June 10, 1993, and has been funded and coordinated by the National Cancer Institute (NCI), in collaboration with the National Institute of Environmental Health Sciences (NIEHS). The multistudy LIBCSP has been investigating whether environmental factors are responsible for breast cancer in Suffolk, Nassau, and Schoharie Counties, New York, and Tolland County, Connecticut. The LIBCSP is part of overall research efforts of the National Institutes of Health (NIH) to investigate the causes of breast cancer and find ways to prevent the disease.

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The LIBCSP consists of human population (epidemiologic) studies, the establishment of a family breast and ovarian cancer registry, and laboratory research on mechanisms of action and susceptibility in the development of breast cancer. (See Appendix B.) Most of the studies were conducted by scientists at major medical research institutions in the Northeastern United States, and most of the results have been reported in peer-reviewed journals. Continuing activities are: a follow-up study on women with breast cancer who participated in the centerpiece case-control study to determine whether certain chemical exposures influence breast cancer outcomes; additional analyses from some studies from which primary findings have been reported; a study on geographic influences on risk for breast cancer; and the breast/ovarian cancer registry, which continues to enroll eligible families and provide researchers a resource for their investigations is ongoing as part of a larger NCI program. In addition, a new research tool was developed, the Geographic Information System for Breast Cancer Studies on Long Island (LI GIS, initially called GIS-H), and is available for researchers to use to investigate relationships between breast cancer and the environment and to estimate exposures to environmental contamination. Geographic information systems (GIS) are powerful computer systems that permit layers of dissimilar information (e.g., geographic, demographic, environmental, and breast cancer data) to be superimposed and analyzed. The total estimated funding for the LIBCSP is \$30,035,000 for fiscal years (FY) 1993 through 2004. (See Appendix C.)

Findings on the primary hypotheses investigating suspect chemical agents and electromagnetic fields (EMFs) have been reported, with the exception of the ongoing follow-up to the centerpiece case-control study. These completed investigations did not find organochlorine compounds or EMFs to be associated with increased risk for breast cancer on Long Island. Exposure to polycyclic aromatic hydrocarbons (PAHs)^a was associated with a moderate increased risk for the cancer, but the finding needs to be confirmed in studies of other populations. Other findings suggested that polychlorinated biphenyls (PCBs)^b may be associated with increased risk for recurrence of breast cancer, but the numbers were small and no association was found with initial occurrence of breast cancer. The follow-up case-control study will provide further insight. Researchers also found that many of the well-known risk factors for breast cancer, such as late age at first birth, were present among Long Island women. The findings from the LIBCSP may offer reassurance to concerned individuals. Nevertheless, LIBCSP investigators continue to conduct additional analyses to explore further possible relationships between environmental exposures and breast cancer.

For Tolland and Schoharie Counties, researchers were not able to conduct valid analyses because the number of women with breast cancer was too few in each location.

This report is organized into eight sections:

- *Introduction* states the Congressional mandate for conducting the LIBCSP and summarizes the response from NCI and NIEHS.
- *Background* provides breast cancer statistics for the concerned counties, and discusses steps taken to conduct the Project and the exposures studied.
- *Research and Findings* describes the findings of the extramural and intramural studies conducted.
- *Geographic Information System for Breast Cancer Studies on Long Island* describes the development of this new research tool.
- *Relevant Non-LIBCSP Research* describes other research that has been conducted on breast cancer and the environment.
- *Community Outreach/Relations* reviews activities that were undertaken to keep the community informed about, and a part of, the Project.
- *Future Directions* describes other NCI and NIEHS research and activities underway to further epidemiologic investigations on environmental causes of breast cancer.

^a PAHs are pollutants caused by incomplete combustion of various chemicals, such as diesel fuel and cigarette smoke.

^b PCBs are a group of organochlorine compounds used widely in coolants and lubricants.

- *Conclusion* summarizes the accomplishments of the LIBCSP.

II. Background

A. Breast Cancer Statistics

Long Island, like other areas of the Northeast, has elevated rates of breast cancer mortality compared to the U.S. average.¹ The incidence rate for breast cancer (newly diagnosed cases per 100,000 females) increased in Nassau, Suffolk, Schoharie, and Tolland Counties between 1986-1990 and 1996-2000, as did rates for New York State and the United States. The percentage of increase for Nassau, Suffolk, Schoharie, and Tolland Counties exceeded that for the United States, but generally was similar to that for New York State as a whole. During the same time period, all of these geographic areas experienced a decline in breast cancer mortality, which likely is attributable to earlier detection and improved treatments. Nationally, rising breast cancer incidence rates during the 1990s and declining mortality rates have been attributed, in part, to increased mammography screening and the dissemination of improved therapies.^c

Incidence and Mortality for Female Breast Cancer per 100,000 Females, 1986-1990 and 1996-2000^d

	Incidence			Mortality		
	1986-90	1996-2000	% Change	1986-90	1996-2000	% Change
Nassau	136.4	145.5	+ 6.7	41.3	32.3	-21.8
Suffolk	130.3	149.1	+14.4	42.8	32.4	-24.3
Schoharie	99.3	111.8	+12.6	37.6	34.3	-8.8
New York State	118.7	133.6	+12.6	37.4	30.1	-19.5
NY State, excluding Nassau and Suffolk	116.1	131.3	+13.1	36.6	29.7	-18.9
United States	130.2	137.1	+5.0	33.0	27.2	-18.0
Tolland	135.1	137.1	+1.0	33.9	22.9	-32.0

^c The U.S. annual average age-adjusted incidence rate for breast cancer continues to increase among white and black women, although the rate of increase has slowed to 0.6 percent per year since 1986. Mortality rates began decreasing in the 1990s, with steeper declines for white women, 2.5 percent per year, than for black women, 1.0 percent per year. Weir HK, Thun MJ, Hankey BF, Ries LA, Howe HL, Wingo PA, Jemal A, Ward E, Anderson RN, Edwards BK. Annual report to the nation on the status of cancer, 1975-2000, featuring the uses of surveillance data for cancer prevention and control. *J Natl Cancer Inst.* 2003;95(17):1276-1299.

^d Rates are age-adjusted to the 2000 census population. Sources of statistics: incidence and mortality rates for New York, New York State Cancer Registry; U.S. and Tolland County mortality rates, National Center for Health Statistics; U.S. and Tolland County incidence rates, Surveillance, Epidemiology and End Results (SEER) Program, NCI.

B. Breast Cancer Epidemiology

Breast cancer is the most frequently diagnosed nonskin cancer among women in the United States. It is the second leading cause of cancer deaths among women (after lung cancer). An estimated 215,990 new cases of breast cancer will be diagnosed in 2004, and about 40,110 women will die of the disease.²

Geographic variation in breast cancer rates has been well documented, both internationally and within the United States. (See Appendix D.) A pattern of elevated mortality rates for female breast cancer extending from the Mid-Atlantic through the Northeastern states has persisted for many years. Established risk factors are believed to be largely responsible.³ Established risk factors for breast cancer are:

- **Age.** The chance of being diagnosed with breast cancer goes up as a woman gets older. A woman over age 60 is at greatest risk.
- **Personal history.** A woman who has had breast cancer in one breast has an increased risk of getting this disease in her other breast.
- **Family history.** A woman's risk of breast cancer is higher if her mother, sister, or daughter had breast cancer, especially at a young age (before age 40). Having other relatives with breast cancer on either her mother's or her father's side of the family may also increase a woman's risk.
- **Certain breast changes.** Some women have cells in the breast that look abnormal under a microscope. Having certain types of abnormal cells (atypical hyperplasia or lobular carcinoma *in situ* [LCIS]) increases the risk of breast cancer.
- **Genetic alterations.** An estimated 5 to 10 percent of all breast cancers can be attributed to genetic factors. Changes in certain genes (BRCA1, BRCA2, and others) increase the risk of breast cancer. In families in which many women have had the disease, genetic testing can sometimes show the presence of specific genetic changes that are related to risk.
- **Reproductive and menstrual history.** The older a woman is when she has her first child, the greater her chance of breast cancer. Women who began menstruation (had their first menstrual period) at an early age (before age 12), went through menopause late (after age 55), or never had children also are at an increased risk. Women who take menopausal hormone therapy (either estrogen alone or estrogen plus progestin) for 5 or more years after menopause also appear to have an increased chance of developing breast cancer. Much research has been done to learn whether having an abortion or a miscarriage affects a woman's chance of developing breast cancer later. Large, well-designed studies have consistently shown no link between abortion or miscarriage and the development of breast cancer.

- **Race.** Breast cancer occurs more often in white women than Latina, Asian, or African-American women.
- **Radiation therapy to the chest.** Women who had radiation therapy to the chest (including breasts) before age 30 are at an increased risk of breast cancer. This includes women treated with radiation for Hodgkin's lymphoma. Studies show that the younger a woman was when she received radiation treatment, the higher her risk of breast cancer later in life.
- **Breast density.** Older women who have mostly dense (not fatty) tissue on a mammogram (X-ray of the breast) are at increased risk of breast cancer.
- **Taking DES (diethylstilbestrol).** DES is a synthetic form of estrogen that was given to some pregnant women in the United States between about 1940 and 1971. (DES is no longer given to pregnant women.) Women who took DES during pregnancy have a slightly increased risk of breast cancer. This does not yet appear to be the case for their daughters who were exposed to DES before birth, although their risk is increased for vaginal cancer. As these daughters grow older, however, more studies are needed to monitor their risk of breast cancer.
- **Being obese after menopause.** After menopause, women who are obese have an increased risk of developing breast cancer. Being obese means that the woman has an abnormally high proportion of body fat. Because the body makes some of its estrogen (a hormone) in fatty tissue, obese women are more likely than thin women to have higher levels of estrogen in their bodies. High levels of estrogen may be the reason that obese women have an increased risk of breast cancer. Also, some studies show that gaining weight after menopause increases the risk of breast cancer.
- **Physical inactivity.** Women who are physically inactive throughout life appear to have an increased risk of breast cancer. Being physically active may help to reduce risk by preventing weight gain and obesity.
- **Alcoholic beverages.** Some studies suggest that the more alcoholic beverages a woman drinks, the greater her risk of breast cancer.

Some risk factors can be avoided or reduced, while others, such as family history, cannot be avoided. Most women who have these risk factors do not get breast cancer. Also, most women who develop breast cancer have no history of the disease in their families. Except for growing older, most women with breast cancer have no strong risk factors.

The reasons for the remaining cases of breast cancer are not understood, and thus, researchers have turned to possible environmental causes for answers. Although public concerns have focused on exposure to environmental hazards, such as pesticides, landfills, industrial chemicals, and electromagnetic fields, at the time the LIBCSP began, the evidence linking them to breast cancer had been negative or inconclusive.

C. Steps Taken

The first phase of the LIBCSP focused on establishing contacts with community groups and with other health- or environmental-related agencies, and locating sources of data and scientific expertise. As part of this process, in January 1994, NCI and NIEHS convened a meeting of representatives of the NCI-designated cancer centers in the New York City region at New York University to stimulate interest in undertaking the LIBCSP. Represented were researchers from the American Health Foundation, Columbia-Presbyterian Cancer Center, Memorial Sloan-Kettering Cancer Center, Albert Einstein College of Medicine, New York University Kaplan Cancer Center, and Cold Spring Harbor Laboratory. The group discussed ways in which their research expertise could be brought to bear on elucidating the problem of breast cancer on Long Island, and was encouraged to submit grant applications to the NIH through its scientific review process.

In the spring of 1994, NCI and NIEHS staff met with breast cancer advocates in Bethesda, Maryland, to discuss community input into the research and participation on the *ad hoc* Advisory Committee.

Ten research projects were funded through new grant awards or supplemental funding of existing grants: two case-control studies on Long Island (Columbia University and subsequently University of North Carolina [UNC] at Chapel Hill, and Stony Brook University); a hospital-based study on Long Island and a case-control study in Schoharie County (American Health Foundation); a case-control study in Tolland County (Yale University); exploratory study on estimating environmental exposures (University of Buffalo); breast cancer screening study (Stony Brook University); Metropolitan New York Registry for families with a history of breast or ovarian cancer (Columbia University); and three laboratory studies on the biology of and susceptibility to breast cancer (Albert Einstein College of Medicine, Cold Spring Harbor Laboratory, and New York University). The aim was to use multiple scientific approaches and study designs to address the problem of breast cancer on Long Island. Hence, although the laboratory studies did not yield Long Island-specific results as had been hoped, they advanced our overall understanding of the cancer. These projects were funded in 1994 and 1995 for periods ranging from 1 to 4 years, with the larger case-control studies receiving extensions. In 2001, a follow-up study to the case-control study by Columbia University/UNC at Chapel Hill researchers was funded (see *Research and Findings* section). The LIBCSP is chiefly an extramurally funded research program, although some research was conducted at NCI (see *Research and Findings* section).

Many new contacts have been made and relationships forged over the years of the LIBCSP with federal, state, and local government groups, including the U.S. Environmental Protection Agency (EPA), U.S. Geological Survey (USGS), Agency for Toxic Substances and Disease Registry (ATSDR), U.S. Census Bureau, New York State Department of Health, Nassau and Suffolk County governments; research and medical institutions; private organizations; and breast cancer advocacy and other community groups. Many sources of expertise have been pursued, particularly with respect to development of the LI GIS where the application of this technology to the study of the environment and breast cancer was largely uncharted.

The LIBCSP arose from concerns raised by Long Island women with breast cancer and their families and friends. NCI and NIEHS responded with an active community relations program to keep residents informed and to provide opportunities for participation in the overall Project. Town meetings and workshops have been hosted, and presentations have been made to community groups. Web sites were established to provide ready access to information.

NCI's Cancer Information Service (CIS) also has assisted. The CIS provides information on cancer and cancer treatment (via the toll-free number 1-800-4-CANCER), a LiveHelp online service (Web site: cancer.gov), and a partnership outreach program. It also has regional offices that serve the entire country. Long Island is covered by Memorial Sloan-Kettering Cancer Center in New York City, which maintains a community outreach office on Long Island. The CIS staff has helped keep the community informed about LIBCSP developments and has provided NCI staff information related to outreach. More detailed information on LIBCSP communications and community relations is provided in the *Community Outreach/Relations* section of this report.

An *ad hoc* Advisory Committee of extramural scientists and community members advised NCI and NIEHS on the Project, and met annually until 1997. The committee was comprised of nine scientists, one health communications expert, and five community members. (See Appendix E.) In addition, each of the two Long Island case-control studies (Breast Cancer and the Environment on Long Island Study, by Columbia University/UNC at Chapel Hill, and EMF and Breast Cancer on Long Island Study, by Stony Brook University) had an external advisory committee.

The LIBCSP is a complex research effort that charted new ground in environmental epidemiology. Assessing environmental exposures and determining their relationship with cancer are difficult. From the Project's beginning, it was clear that new technologies would need to be developed to enable scientists to measure and analyze certain exposures, and then determine their relevance to breast cancer. New biological markers of individuals' cumulative exposures over many years were, and continue to be, needed. Computer systems capable of analyzing multiple environmental exposures in geographic areas and breast cancer incidence were needed. The LIBCSP investigators made progress in these areas and developed new environmental measurement and laboratory techniques, and explored new ways to study the relationship between the environment and breast cancer. Much remains to be learned, however, and NCI and NIEHS have ongoing programs to develop methods for accurate determination of chemical exposures for critical periods in a woman's lifetime beginning with early life exposures that may be relevant to breast cancer development.

The science of GISs, when used as tools to study relationships between environmental factors and cancer, presents many challenges. Only with recent advances in computer hardware, software, and increased availability of geocoded health and environmental data (data tagged to specific location[s]), have GISs come into use in public health investigations and health promotion.

To implement the LI GIS, a 1-year feasibility study was conducted by Brookhaven National Laboratory, and a working group of university and federal government experts then assisted NCI to prepare a detailed Request for Proposals (RFP) to develop and implement the tool. In 1999, NCI awarded the contract for the LI GIS to develop the tool for use in the study of potential relationships between the location of breast cancer cases and sources of pollution. An Oversight Committee for the LI GIS comprised of 12 scientists and 5 community members guided development of the tool. (See Appendix F.)

The lead NIH scientists for the LIBCSP are Deborah Winn, Ph.D., Acting Chief, Clinical and Genetic Epidemiology Research Branch (CGERB), Epidemiology and Genetics Research Program, (EGRP), Division of Cancer Control and Population Sciences (DCCPS), NCI, and Gwen Collman, Ph.D., Chief, Susceptibility and Population Health Branch (SPHB), Division of Extramural Research and Training (DERT), NIEHS. The LI GIS is managed by an NCI team that includes Dr. Winn; Burdette (Bud) Erickson, M.Sc., Project Officer; Julian Smith, Program Analyst; Edward Trapido, Sc.D., Associate Director of EGRP; Theresa Shroff, contract officer; and Linda Anderson, M.P.A., LIBCSP Director of Communications. Kumiko Iwamoto, M.D., Dr.P.H., EGRP, was the NCI Program Director for many of the grants. Noreen Aziz, M.D., Office of Cancer Survivorship, DCCPS, is the NCI Program Director for the follow-up study to the centerpiece case-control study at UNC at Chapel Hill.

D. Primary Agents Studied

The LIBCSP researchers focused their attention on environmental agents for which preliminary studies suggested that the exposures might be associated with breast cancer causation, and for which laboratory methods existed, or could be developed, to determine exposures that may have occurred many years earlier, when breast cancer would have been developing. A major problem in cancer epidemiology is the limited number of biomarkers that provide evidence of past human exposures. Indicators do not exist for most past exposures, and an exposure may clear the body in hours or in a day, without leaving evidence detectable by current scientific methods. For cancer, which has a long latency, exposures that occurred long before diagnosis are key to analysis.

The chief environmental agents investigated were: 1,1,1-trichloro-2,2-bis (*p*-chlorophenyl) ethane (DDT), or its metabolite dichloro-2,2-bis (*p*-chlorophenyl) ethylene (DDE); PCBs; PAHs; and EMFs. When the LIBCSP was launched, there were very few results from animal experiments or human studies that pointed to likely research possibilities. Two preliminary reports of blood analyses in small groups of women had suggested that certain pesticides in the environment might increase the risk of breast cancer.^{4,5} This observation seemed plausible based on earlier experimental, clinical, and epidemiologic data that associated hormones, particularly estrogen, with breast cancer risk, and some pesticide compounds were known to be chemically similar to hormones.

The suspected pesticides, classified as organochlorines, include DDT/DDE and PCBs. These chemicals are known as xeno-estrogens because they exert an estrogenic effect, though weak, on

human tissue.⁶ Because estrogenic activity is known to be associated with breast cancer risk, the focus on xeno-estrogens was thought to be a potential field of research that might yield conclusive results.

DDT use began in the United States in the 1940s, and it continued widely until 1972 when it was banned. Although no longer used in the United States, the compound takes many years to disappear from the environment. The concern with DDT and its metabolite DDE grew when it was learned that they persist in the blood and accumulate in the human body, specifically in adipose (fat) tissue. Numerous studies have shown that DDT accumulates in breast tissue and that infants are exposed to it during lactation.⁷ It has not yet been determined whether DDT causes cancer in humans, although it was classified by the International Agency for Research on Cancer (IARC) as “possibly carcinogenic” based on animal studies.⁸

PCBs are a group of more than 200 related compounds, called congeners, that have been used widely as coolants and lubricants in transformers, capacitors, and other electrical equipment. Products containing PCBs are old fluorescent lighting fixtures, electrical appliances containing PCB capacitors, old microscope oil, and hydraulic fluids. The manufacture of PCBs stopped in the United States in 1977 because of evidence that they accumulate in the environment and cause harmful effects. Breast cancer risk from PCBs has been studied for more than 30 years, but when the LIBCSP studies were initiated, the data were inconclusive. PCBs are known to have estrogenic properties in humans, but the effects are weak.⁵ Importantly, individual PCB congeners are classified as estrogenic, anti-estrogenic, or neither based on data from numerous research studies.⁹ This may explain, to some degree, why results of studies evaluating the effect of PCBs on breast cancer have been conflicting.

After the LIBCSP was underway, findings from other research emerged that suggested the organochlorine compound dieldrin may be associated with increased risk for breast cancer and poorer survival from the disease.^{10,11} As a result, dieldrin was added to the analyses being conducted in the Breast Cancer and the Environment on Long Island Study.

PAHs are a group of ubiquitous pollutants caused by incomplete combustion of various chemicals including diesel fuel and cigarette smoke. A critical step in carcinogenesis initiated by PAHs is the attachment of PAH metabolites to DNA-forming complexes called DNA adducts. The relationship between adducts formed from environmental risk factors, such as smoking, and development of breast cancer has not yet been determined. Insights into the extent of damage and mechanism of initiation of carcinogenesis will help to provide a more comprehensive understanding of breast cancer, and for this reason, PAHs were of interest.

EMFs are the result of living in modern times. Wherever electricity is used, a relative magnetic and electric field is produced. This includes the household where appliances, CD players, televisions and radios, and the general wiring in the house all produce EMFs. Of public concern are the EMFs produced by high-voltage transmission wires running through neighborhoods. EMFs became a suspected carcinogen when animal experiments demonstrated EMF suppression of melatonin secretion.¹² Melatonin suppresses mammary tumorigenesis in rats and blocks

estrogen-induced proliferation of human breast cancer cells *in vitro*. It was reasoned, therefore, that decreased melatonin production might lead to increased risk of breast cancer. Melatonin is a hormone produced in response to a lack of light by the pineal gland, which is located at the base of the brain. Melatonin levels typically are low during the day, and increase at night, peaking between 2:00 and 4:00 a.m. Exposure to light-at-night (for example, as in shift work) or to higher levels of magnetic fields are thought to suppress this normal, nocturnal rise in melatonin. Melatonin levels are believed to be inversely related to estrogen levels, in that when melatonin levels are low, estrogen levels are high and vice versa. Therefore, if light-at-night or magnetic field levels suppress the normal, nocturnal rise in melatonin, estrogen levels subsequently would be increased. Because increased levels of estrogen are hypothesized to increase the risk of breast cancer, this suppression of melatonin by either light-at-night or magnetic fields possibly could increase the risk of breast cancer.

Epidemiologic studies assessing the effect of EMF exposures in occupational settings and by histories of electric blanket use had been inconclusive when the LIBCSP began.^{13,14,15,16} The 1999 NIEHS report on power-line frequency electric and magnetic fields presented a summary of the literature on breast cancer associations and noted the lack of evidence of any relationship.¹⁷ The challenge of EMF research has been accurate assessment of total exposure, particularly because the general population likely is exposed, at low doses, to ubiquitous and multiple sources.

The LIBCSP also investigated the role of established risk factors for breast cancer. This information and examination provides a more detailed picture of the breast cancer situation in the study areas.

III. Research and Findings

Extramural studies conducted by university and New York State government scientists are described first, followed by studies conducted at NCI. The title of each study is given, followed by the name of the principal investigator, his/her institutional affiliation, and then a summary of the study design and findings, if completed. The principal investigator is the scientist who conceived of and leads the study. A compendium of the reports published on the studies also is provided. (See Appendix G.)

A. Extramural Research

Breast Cancer and the Environment on Long Island Study and Breast Cancer and the Environment on Long Island Follow-up Study

Marilie Gammon, Ph.D., UNC at Chapel Hill, North Carolina

(Dr. Gammon began the study at Columbia University and relocated to UNC in 1999.)

The centerpiece of the LIBCSP, the Breast Cancer and the Environment on Long Island Study, has been the investigation of whether certain environmental contaminants increase risk of breast cancer among women on Long Island. The primary aims were to determine if the

organochlorine compounds DDT, PCBs, chlordane, and dieldren, and PAHs are associated with risk for breast cancer among women on Long Island.

Principal Investigator Dr. Gammon began the study while at Columbia University, New York. In 1999, she relocated to the UNC at Chapel Hill where she continued to lead the study. The study has been a collaborative effort involving numerous New York City and Long Island researchers. (The study also is sometimes referred to as the Columbia case-control study or the LIBCSP itself.)

The researchers found that organochlorine compounds were not associated with the elevated rates of breast cancer on Long Island.¹⁸ They also found that exposure to PAHs was associated with a modest (50 percent) increased risk for breast cancer.¹⁹ (Compared to other known risk factors for cancer, a 50 percent increase in risk is modest. For example, smoking increases the risk of developing lung cancer by 900 percent to 1,000 percent. A family history of breast cancer increases risk by 100 percent to 200 percent.) These findings were reported in 2002.

The finding on PAHs is consistent with the few, much smaller epidemiologic studies and suggests the need for additional research in other populations. It is possible that breast cancer risk in some individuals may be associated with organochlorine exposures because of individual differences in metabolism and ability to repair DNA damage, and the researchers are pursuing this in other research in the study population.

In addition, many of the well-known breast cancer risk factors were confirmed. These risk factors included increasing age, having a family history of breast cancer, having a first child at a later age (age 28 or older in this study), never having given birth to a child, and having higher income.²⁰ Some recognized risk factors were not found to be associated with increased risk for breast cancer among all women in the study. These included early age at beginning of menstruation (menarche) and having attained a higher level of education. The researchers are conducting more detailed analyses to further explore these results.

Other published reports by the research group focused on necessary methods development. They include papers on assessment of variation in DDE and PCB levels over time, comparison of serum and adipose tissue levels of chemical compounds, and identification of groups of similar PCBs by, for example, estrogenicity.^{21,22,23}

Study Description

The population-based, case-control study included 1,508 women living in Nassau and Suffolk Counties who were newly diagnosed with *in situ* or invasive breast cancer during a 1-year period beginning August 1996 (cases), and a similar number of women who did not have cancer (controls). (*In situ* breast cancer is early cancer that has not spread to neighboring tissue.) The study participants were asked to answer two questionnaires, and the majority provided pre- and post-treatment blood samples and urine specimens.

The main questionnaire asked the women about their pregnancy and occupational histories, residential history in Nassau and Suffolk Counties, use of pesticides in and around the home or farm, use of electrical appliances, lifetime history of eating smoked or grilled foods, active and passive cigarette smoking history, alcohol consumption, medical history, menstrual history, use of hormones, family history of cancer, body-size changes by decade of life, lifetime participation in recreational physical activities, and demographic characteristics such as race/ethnicity. Women also were asked to complete a food questionnaire.

A subset of the study population who had lived in their current homes for 15 years or more was invited to participate in environmental sampling of house dust, tap water, and yard soil to test for organochlorine compounds and PAHs. A random sample of white women who had met the residency requirement was invited to participate. All study participants who identified themselves as African American or black and who met the residency requirement were invited to participate. Of the total study population, 383 cases and 429 controls participated in the home study.

Blood and urine samples from 400 of the cases with invasive cancer, 200 of the cases with *in situ* disease, and 400 of the controls were randomly selected from the study population and analyzed. Laboratory analyses were conducted to measure organochlorine pesticides and PAH-DNA adducts in blood. The level of binding of PAHs to DNA (forming what are called PAH-DNA adducts) was measured in blood samples; formation of PAH-DNA adducts is believed to be necessary for cancer development. For the home study, samples were assayed for pesticides and PAHs. (An assay is a laboratory test to find and measure the amount of a specific substance.) The blood and urine samples of all African American or black study participants were included in the analyses to increase the data available for this group.

Continuing Research

The researchers currently are analyzing the blood samples that were not part of the initial analyses for PAH-DNA adducts to confirm their initial finding; the urine samples for estrogen metabolites, which are of interest because differences in the way women metabolize estrogen may be related to risk for breast cancer; questionnaire data on pesticide use; heterocyclic aromatic amines (HAA) and PAHs from food sources; and data from the home study. HAAs are carcinogenic chemicals formed from the cooking of muscle meats such as beef, pork, fowl, and fish. Findings from this group of analyses are expected in 2004 or later. Other analyses are underway on weight gain, diet, alcohol consumption, recreational physical activity, DNA repair gene polymorphisms (variations in DNA sequence) in relation to DNA adduct formation, and oxidative stress. Oxidative stress is a term used to describe a type of damage to the body due to products derived from the metabolism of oxygen.

A recently completed analysis on environmental tobacco smoke (ETS) did not provide strong support for a relationship between exposure and increased risk for breast cancer, except perhaps for specific subgroups such as nonsmoking women with long-term exposure from a smoking spouse.²⁴ Risk was increased twofold among nonsmoking women who lived with a smoking spouse for more than 27 years. However, there was no dose-response relationship; that is, the

risk did not increase with increasing years of exposure. Findings on ETS and breast cancer have been inconsistent, and investigations in the area continue to be of interest because some tobacco smoke constituents are known mammary carcinogens.

The grant for the Breast Cancer and the Environment on Long Island Study also provided funds for a feasibility study to develop a geographic modeling system to estimate historical exposure of study participants to airborne PAHs from traffic emissions. Use of geographic modeling is relatively new to environmental epidemiology. A major purpose of the method is to use available data to estimate environmental exposures for individuals at specific geographic locations and times. Development of the methodology was led by Maureen Hatch, Ph.D., while at Columbia University, and the research is completed. One report on the system has been published²⁵, and a second report was submitted in late 2003 for publication in a scientific journal. (Dr. Hatch joined NCI's intramural research program in 2003.)

Dr. Gammon and colleagues continue to follow the women with breast cancer who participated in the study to determine whether organochlorine compounds (including DDT/DDE, PCBs), PAH, and lifestyle factors influence survival of Long Island women diagnosed with the disease. For this LIBCSP research, titled the Breast Cancer and the Environment on Long Island Follow-up Study, Dr. Gammon received a 4-year grant from NCI in 2001.

Spinoff Studies

Numerous spinoff studies are underway using the population, data, or specimens from the initial study. These studies are funded by various organizations and are independent of the LIBCSP. Investigators who are interested in conducting research using the data and/or specimens from the initial study may contact Dr. Gammon, who has a Data Sharing Committee comprised of collaborating scientists and one community member.

These spinoff studies include the following:

- Dr. Gammon is examining p53 protein in tumor tissue. p53 is a gene that normally regulates the cell cycle and protects the cell from damage to its genome. Mutations, or changes, in this gene cause cells to develop cancerous abnormalities. This p53 study is funded by the U.S. Department of Defense (DOD).
- Habibul Ahsan, M.D., of Columbia University, New York, and colleagues are examining whether certain common variations in the sequence of DNA involved in the biosynthesis and metabolism of estrogen and environmental carcinogens are associated with risk for breast cancer. This study is funded by DOD, NCI, and the Cancer Research Foundation of America.
- Regina Santella, Ph.D., also of Columbia University, and colleagues are examining PAH-DNA adducts in the tumor tissue of breast cancer patients from the Breast Cancer and the Environment on Long Island Study, to learn more about the etiology of breast cancer. This study is funded by the Breast Cancer Research Foundation.

- Dr. Gammon and Dr. Santella are examining the role of variants in genes involved in oxidative stress related to environmental contaminants. This research is funded by NCI.
- Rebecca Cleveland, of UNC at Chapel Hill, and Dr. Gammon are examining variants of insulin-like growth factor (IGF-1) in relation to risk for breast cancer. IGF-1 is known to cause proliferation of human breast cancer cells, and also to prevent the body's clearing of old and damaged cells. This may cause increased growth of tumor cells, in addition to accumulation of breast cells that have mutated to cancerous forms. The study is funded by DOD.
- Jia Chen, Ph.D., of Mount Sinai School of Medicine, New York, and colleagues are studying whether variations in genes involved in the metabolism of folate are related to risk for breast cancer. Folate deficiency may be associated with increased risk for breast cancer. The study is funded by DOD.

Electromagnetic Fields (EMF) and Breast Cancer on Long Island Study

M. Cristina Leske, M.D., M.P.H., Stony Brook University, State University of New York, Stony Brook, New York

Dr. Leske and colleagues conducted a population-based, case-control study to evaluate whether EMFs are associated with increased risk for breast cancer. In 2003, the researchers reported finding no association between residential exposure to EMFs and risk for breast cancer.^{26,27}

EMF levels, as measured by in-home spot, 24-hour, ground-current measurements, and wire codes, did not differ between women who were diagnosed with breast cancer (cases) and women who did not have the disease (controls). Furthermore, no differences were observed between the two groups when the data were analyzed controlling for age, family history of breast cancer, personal history of benign (noncancerous) breast disease, number of children (parity), and education.

The study consisted of 576 women (cases) who were newly diagnosed with breast cancer during the 1-year period beginning in August 1996, and 585 women (controls) who did not have the disease. All of the women were younger than 75 years of age and had resided in their current homes in Nassau and Suffolk Counties for at least 15 years before the time of diagnosis of breast cancer (cases), or at the time they were identified (controls) for the study. The study population was drawn from the larger study population of the Breast Cancer and the Environment on Long Island Study. (The participation rate was low among women age 75 and older in the larger study, thus they were not included in the EMF study.)

The researchers conducted a comprehensive home assessment of the study participants' exposure to EMFs through personal interviews and by taking a variety of EMF measurements within and around the outside of the home. The 24-hour, spot, and ground-current measurements were taken with specially designed equipment to measure EMFs. The measurement methods were based on the results of a pilot study, which is described in another scientific paper.²⁸ EMFs were measured in the following ways:

- 24-hour measurements were taken in the bedroom and the room the participant spent the most time in, aside from the kitchen (living room, den, most lived-in room);
- Spot measurements were taken at the front door, in the bedroom, and the most lived-in room;
- Ground-current magnetic fields, which are sometimes present in a home's electrical grounding system, were measured at the center of the bedroom and the most lived-in room; and
- Wire coding (or wire mapping) was performed to classify the type of wiring surrounding a home and the distance from this wiring; this information was coded using the Wertheimer-Leeper²⁹ and Kaune-Savitz systems.³⁰

These findings are similar to those reported by scientists at the Fred Hutchinson Cancer Research Center in 2002.³¹ Both of these studies included a comprehensive set of in-home measurements of EMF exposure and wire codes. In addition, Dr. Leske's study included ground-current magnetic field measurements. Furthermore, the study included only long-term residents, with the objective of assessing exposures over an extended time period. The study also is notable for its large sample size and high participation rates, and use of the best available methods to estimate past exposure to magnetic fields in the home.

In additional analyses, the researchers found no association between use of electric blankets and risk of breast cancer.³² No trends were seen with increased duration of use, frequency of use, or other indicators of more intense exposure to EMFs. Also, electric blanket use was not associated with hormone receptor status of the tumor. The findings from these very comprehensive analyses are consistent with results from most other studies. In an editorial accompanying publication of these results, Dale Sandler, Ph.D., of NIEHS, commended the study for its high quality.³³

Further EMF analyses are underway based on the extensive information collected from study participants. The research team plans to publish additional papers on findings related to light-at-night and shift work, occupational exposures, and electrical appliance use when analyses of data are completed.

Epidemiology of Breast Cancer and Serum Organochlorine and Serum Organochlorine Compounds and Breast Cancer on Long Island

Steven D. Stellman, Ph.D., Columbia University

(Dr. Stellman was formerly with the American Health Foundation, Valhalla, New York.)

Dr. Stellman, while at the American Health Foundation, and colleagues conducted a hospital-based, case-control study to investigate risk for breast cancer in relation to levels of organochlorine compounds such as DDT and PCBs. In 2000, they found that increased risk for breast cancer was not associated with past exposure to organochlorine compounds.³⁴ The lack of

association held both for women whose tumors were estrogen-receptor positive, as well as for women whose tumors were estrogen-receptor negative.

The study included 232 women who had surgery for breast cancer (cases) and 323 women who had surgery for noncancerous breast disease or for conditions unrelated to the breast (controls). Of the cases, 199 had invasive breast cancer, and 33 had carcinoma *in situ*. The women in the control group had had surgeries involving their gallbladders, removal of lipomas, abdominal hernias, osteoarthritis, and other conditions unrelated to the breast. The women were treated between 1994 and 1996. Both groups were similar in education, race, body mass index (a composite measure of weight and height), age at first live birth of a child, and county of residence.

The women had received their care at Long Island Jewish Medical Center, New Hyde Park, New York, and North Shore University Hospital, Manhasset, New York, which are the two largest hospitals serving the Long Island population. Fifty-seven percent of cases (128 women) and controls (186 women) lived in Nassau or Suffolk County. The other study participants lived in New York City, primarily in Queens County. There were no major differences in blood levels of the organochlorine compounds and PCBs, when the data were compared, between women living in Nassau and Suffolk Counties with residents of Queens County. Also, no significant differences in exposures were seen between residents of Nassau and Suffolk Counties.

The study participants provided adipose (fat) tissue obtained at surgery and blood samples, and answered a questionnaire about their medical and reproductive history, diet, smoking, and other lifestyle factors. Adipose tissue was used for this analysis because the fat-soluble organochlorine compounds accumulate and are stored in body fat for many years. They are excreted very slowly from the body, making it possible to look for evidence today of exposures that have occurred over a long period. The adipose tissue from the breast cancer patients was obtained prior to chemotherapy or radiation treatment for the disease.

The study focused on 7 organochlorine pesticides and 14 congeners (types) of PCBs. The organochlorine pesticides or their products that were measured were: DDT and two related chemicals, DDD and DDE (the main breakdown product of DDT in the environment and in the body); oxychlordane and trans-nonachlor, which are products of chlordane, a once-common termite treatment; and two pesticides, β -hexachlorocyclohexane (β -HCH) and hexachlorobenzene (HCB).

Cases and controls had comparable levels of total organochlorine pesticides and total PCBs in their adipose tissues, after adjusting for age and body mass. There was no association between breast cancer risk and levels of total pesticides or total PCBs. The researchers did find an apparent association with increased risk for breast cancer only with the PCB congener 183, which accounts for about 9 percent of total PCBs. Little is known about this compound's toxicity, except that it weakly induces enzymes that may activate some carcinogens. No association, however, was found between risk for breast cancer and the most abundant PCB congener, 153, which is a much stronger inducer and which also has been found to have

estrogenic properties. The meaning of the finding for congener 183 is unclear, and the observation needs to be confirmed in other studies now in progress. The research team did not confirm a previously reported association with PCB congener 188.

The researchers continued to follow the study population to determine whether survival or recurrence of breast cancer may be related to body burden of organochlorines. In 2003, they reported a threefold increased risk for recurrence of breast cancer among women who were in the highest third for total concentration of PCBs as measured in adipose tissue. This finding is based on small numbers, and contrasts with the researcher's earlier study that showed no effect of organochlorine compounds on risk for breast cancer. Additional research will be needed to pursue this possibility, and may be possible in Dr. Gammon's Breast Cancer and the Environment on Long Island Follow-up Study. An increased risk for recurrence was not found for women who were in the upper tertile of total pesticide concentrations. The analysis was based on data from 224 women from the initial study group. The mean follow-up time since surgery for breast cancer was 3.6 years.³⁵

The researchers also obtained adipose tissue and questionnaire data on women who received their treatment for breast cancer from Bassett Healthcare, Inc., which serves Schoharie County, and controls. The number of women diagnosed with breast cancer from Schoharie County was too small to permit a valid analysis.

In earlier pilot research for the study, Dr. Stellman and colleagues published results of a systematic study of correlations between adipose tissue and serum levels of organochlorine compounds.³⁶ The analysis validated that either tissue or blood can be used to assess a woman's body burden of organochlorine compounds, a point that has sometimes been challenged. Furthermore, the researchers say that they demonstrated that the "profile" of individual organochlorine compounds found in human tissue was similar to that found in animals, such as fish and birds trapped in wildlife, suggesting similar environmental sources of exposure.

Organochlorine Compounds and Risk of Breast Cancer

Tongzhang Zheng, M.D., Sc.D., Yale University, New Haven, Connecticut

Dr. Zheng and colleagues conducted a hospital-based, case-control study in Connecticut to investigate risk for breast cancer associated with exposure to organochlorine compounds. The overall study is considered LIBCSP-related because of its potential relevance. The LIBCSP-specific component was a pilot, case-control study focusing on Tolland County, Connecticut. The number of women diagnosed with breast cancer in the county was too small to conduct a valid analysis.

In the Connecticut study, levels of organochlorine compounds were measured in breast adipose (fatty) tissue and blood serum obtained from women who had surgery or biopsies for breast cancer or benign breast disease. The organochlorine compounds examined were: HCB, β -BHC, DDT/DDE, and PCBs. The researchers did not find an increased risk for breast cancer associated with exposure to any of these agents. The analyses included 304 women who had

breast cancer (cases), and 186 women who had benign breast disease (controls) who were treated at Yale-New Haven Hospital between 1994 and 1997 and who were ages 40-79. Study participants also provided medical and diet histories, and information on alcohol use, cigarette smoking, and other environmental exposures. The findings were published in 1999 and 2000.^{37,38,39,40,41}

Environmental Exposures and Breast Cancer on Long Island

Erin O’Leary, Ph.D., Stony Brook University, State University of New York, Stony Brook, New York

(Dr. O’Leary began the research while at the University of Buffalo, Buffalo, New York.)

Dr. O’Leary, while at the University of Buffalo, conducted a nested, case-control study to determine if residence in close proximity to hazardous waste sites, toxic release inventory sites, prior land use (for example, farm land), and exposure to various chemicals in drinking water may be associated with breast cancer on Long Island.

The study population was selected from a cohort of New York State residents in 1980, established by investigators at the University at Buffalo, who had lived at least 18 years in their current residences and had completed a mailed questionnaire. Within the cohort, 3,097 women from Long Island answered the questionnaire. From this Long Island group, data on 105 women who had been diagnosed with breast cancer (cases) between 1980 and 1992 were compared to data on 210 randomly selected Long Island women who did not have breast cancer (controls), and who were age and race matched to cases.

Because there is no proven way to measure an individual’s historical environmental exposure to most chemicals in the environment, Dr. O’Leary relied on proxies to estimate exposure. She linked data on each woman’s residence with data on historical land use, drinking water, and proximity to hazardous waste sites and toxic release inventory sites, and estimated historical exposures to organochlorine and carbamate pesticides, solvents or volatile organic compounds (VOCs) (e.g., tetrachloroethylene, trichloroethylene, and 1,1,1-trichloroethane), nitrates, and metals (cadmium, chromium, and arsenic). Geographic information software was used to calculate the distance between residences and the point sources of pollution.

Findings from this exploratory study, which were reported from 1999 through early 2004, are as follows:

- Women who lived within 1 mile of hazardous waste sites containing organochlorine pesticides were found to have an increased risk for breast cancer, after adjusting for known risk factors. No association was found between breast cancer and pesticides detected in drinking water or residence on or near agricultural land. Women who lived on or near agricultural land and who were nulliparous (never given birth) or had an older age at first birth had an increased breast cancer risk, compared to women who did not live on or near agricultural land and who had a younger age at first birth. The small sample size limited the study power, and the confidence intervals were wide, which means the

findings could be due to change. These findings suggest the need for additional research on the topic.^{42,43,44,45}

- No association was found between increased risk for breast cancer and exposure to VOCs in drinking water, or residing in close proximity to hazardous waste sites and toxic release inventory sites containing these compounds.⁴⁶ A recent hypothesis suggests that VOCs may be transformed in the breast fat tissue, excreted into the ductular systems, and may initiate or promote breast carcinogenesis.⁴⁷
- No association was found between increased risk for breast cancer and levels of nitrates or metals in drinking water. None of the wells in the water districts studied exceeded the maximum contaminant levels for these compounds allowed by the U.S. EPA. Also, risk for breast cancer was not associated with living within 1 mile of hazardous waste or toxic release inventory sites containing metals.⁴⁸ Nitrates were studied because they have been linked to other cancers, but not specifically to breast cancer.⁴⁹ One occupational study indicated a slightly increased risk for breast cancer in women exposed to metals.⁵⁰ In another study, the metal cadmium was found to increase the growth of human breast cancer lines in cell culture and may have estrogenic activity.⁵¹ Results of a recent study show that cadmium has estrogen-like activity in rats (*in vivo*).⁵²

Reducing Barriers to Use of Breast Cancer Screening

Dorothy S. Lane, M.D., Ph.D., Stony Brook University, State University of New York, Stony Brook, New York

Dr. Lane investigated whether a telephone counseling intervention aimed at women who are known to underuse breast cancer screening can, with or without an accompanying educational intervention for their physicians, increase use of breast cancer screening.^{53,54,55,56} She found that women who had a previous mammogram at the start of the study and who subsequently received telephone counseling were more likely to become regular mammography users than women who did not receive counseling. In addition, the findings suggested that the educational intervention for physicians is associated with initiation of mammography use among women who have never had a mammography. More research with larger samples is needed to confirm this finding.

The study found that women who had a previous mammogram at the start of the study and who received telephone counseling were 40 percent more likely than women who did not receive counseling to become regular mammography users by the end of the study.^{57,58} Greater reductions in perceived barriers to mammography were associated with receiving telephone counseling. Telephone counseling did not appear to be effective among women who never had a mammogram. Data suggested that the physicians continuing medical education (CME) intervention, however, has potential for initiating mammography use among women who never had a previous mammogram (described later). Further study with larger samples is needed to confirm this finding.

In a first step of the study, Dr. Lane and colleagues surveyed more than 8,900 Long Island women, ages 50-80, by telephone about their use of breast cancer screening, and more than 540 doctors by questionnaire. The researchers identified more than 3,400 women who had not received mammograms in the past 2 years and the past 2 years prior to that. Forty-five percent of women in the 65 years-of-age and older age group and 34 percent of women in the 50 to 64 years-of-age group were found to underuse mammography. The chief reasons given for not getting mammograms were procrastination and not believing a mammography was needed—the latter reason given more frequently by women in the older age group. The researchers found that more than 80 percent of the women who were underusers of mammography had less than a college degree, the majority (58 percent) had family incomes of less than \$35,000, and most were homemakers or retired.

During the intervention phase of the study, the effectiveness of telephone counseling and of physician education was tested. An annual mailing alerted women that they would be called by the Early Detection Guidelines Education (EDGE) Project and encouraged them to go for a mammogram. Three annual mailings were conducted during this intervention period and included educational materials and incentives to promote screening. A 3-month period elapsed, following each educational mailing, before initiating telephone counseling of women who did not return the response sheet to allow them time to obtain a mammogram if they were prompted by the mailings. In the intervention group, 1,165 women who were underusers reported obtaining 597 mammograms during the first year of the intervention, and 615 mammograms during the second year of intervention, for a total of 1,195 mammograms.

A quality-control evaluation also was conducted of a sample of 117 counseling calls for the telephone counseling intervention. Seventy-one percent of women who were contacted reported that the calls were “entirely reassuring,” and 71 percent of the women said the calls were “entirely helpful.” In addition, 65 percent of the women said that they felt “entirely encouraged” by the EDGE counselor to have a mammogram in the future. Among women who mentioned a barrier to mammography, 64 percent reported that after discussing it with the EDGE telephone counselor, the barrier would not keep them from getting a mammogram in the future.

Ninety-three physicians obtained the in-office CME intervention from a study educator that included three modules: (1) office systems, (2) behavioral counseling, and (3) revisiting physical examination of the breast.⁵⁹ The in-office intervention also included an optional follow-up visit with the office staff and a subsequent visit by a patient.

As an adjunct to the educator office visit, the researchers developed a workbook that also can be used as a freestanding self-instructional CME activity. The workbook was mailed to those physicians in the intervention group who did not receive an in-office visit. Physicians’ anonymous evaluations of the in-office intervention were very positive.

The researchers found that self-reported overall recognition of the need for breast cancer screening improved for a greater proportion of physicians in the intervention group, especially among those who received the in-office CME intervention, compared to physicians who did not

receive the intervention. Recognition of the need for education about clinical breast examinations also declined, but use of provider reminder systems, preparedness to counsel women about clinical breast exams, and recognition of age as an important risk factor for breast cancer improved in more intervention physicians than control physicians. Dr. Lane's findings as described above were reported in 1999 and 2002.

Metropolitan New York Registry for Families With a History of Breast or Ovarian Cancer
Ruby T. Senie, Ph.D., Columbia University, New York, New York

The Metropolitan New York Registry for families with a history of breast or ovarian cancer invites participation of families who have a history of either or both of these cancers to participate. The Registry is one of six international sites funded by NCI to provide a major resource of data and biospecimens from high-risk families to be used for research purposes. This readily available resource enables investigations into the causes of breast and ovarian cancer, familial susceptibility, and the impact of environment and lifestyle on the development of these tumors.

Individuals who are interested in learning more about the Registry or in enrolling are invited to call 1-888-METRO-08. From 1997 through 2000, an additional recruitment location for Long Island was available at Stony Brook University Hospital and Medical Center. The Registry has reached its goal for numbers of families enrolled, but continues to seek the participation of more relatives per family and more families of African American, Hispanic, and Asian heritage. Family members of both sexes, with and without a history of cancer, are needed. Individuals also may learn about the Registry from its Web site: www.metronyregistry.org.

Participants are asked to contribute personal health information, blood, and urine samples. All information is kept confidential, and all data and specimens have identifying information removed. As of July 2003, 1,196 families, including 4,292 men and women, have enrolled in the Registry, and the number continues to increase steadily.

A component of the Registry offers genetic counseling and testing for BRCA1 and BRCA2 gene mutations for interested families. Mutations of these genes have been associated with increased risk for cancer of the breast and ovaries, and certain other cancers. Registry participants may want to know if they carry a genetic risk of breast and/or ovarian cancer to use in guiding their decisions about screening and options for disease prevention.

Recruitment to the Registry began in January 1997. In 2001, NCI awarded Columbia University a grant to fund the Registry for 5 more years as one of group of six international family cancer registries funded by the Institute. The funding supports additional recruitment of minority families, and follow-up interviews with participating families to keep information current on occurrence of cancer among family members.

Studies conducted through the Registry focus on identification and characterization of breast and/or cancer susceptibility genes; definition of gene-gene and gene-environment interactions in cancer etiology; and cooperative research on the translational, preventive, and behavioral aspects

of such findings. These studies are not limited to Long Island families. One study that directly builds on LIBCSP research is described in *Future Directions*.

Estrogen Metabolites as Biomarkers for Breast Cancer Risk

(also known as Breast Cancer Risk and Inducibility of P450s)

H. Leon Bradlow, Ph.D., Strang Cancer Prevention Laboratory, New York, New York

Long Island researchers investigated whether differences in the way women's bodies process the natural hormone estrogen may be related to breast cancer risk. Estrogen is metabolized by two main, competing pathways, either to 2-hydroxyestrone or to 16 α -hydroxyestrone. Earlier studies suggested that the balance between the estrogen metabolite 16 α -hydroxyestrone (the "bad" metabolite), which has been associated with breast cancer, and 2-hydroxyestrone (the "good" metabolite), which has not, may affect risk for the disease. Dr. Bradlow and Geoffrey Kabat, Ph.D., then with Stony Brook University, examined the ratio between the two metabolites in urine. They found that postmenopausal women with very low levels of the "good" metabolite relative to the "bad" metabolite had a greatly increased risk of breast cancer, compared to women with high levels of the "good" metabolite. Because of the small number of study participants, further research is needed to confirm the findings. The findings were published in 1997.⁶⁰ Dr. Gammon's Breast Cancer and the Environment on Long Island Study includes an analysis of estrogen metabolites in urine, and a similar study is being conducted through the Metropolitan New York Registry (see *Future Directions* section).

Regulation of Scatter Factor Expression in Breast Cancer

Eliot M. Rosen, M.D., Ph.D., Long Island Jewish Medical Center, Albert Einstein College of Medicine, New Hyde Park, New York

Dr. Rosen and colleagues evaluated how scatter factor, a growth factor, may regulate the growth of human breast cancers. Most human breast cancer cells contain high levels of the receptor for scatter factor, which means that, in the laboratory, breast cancer cells will multiply vigorously in the presence of the growth factor. Dr. Rosen and his colleagues found that scatter factor causes human breast cancer cells to move faster and to be more invasive in cell cultures. The growth factor induces the breast cells to produce an enzyme that degrades tissue, thus facilitating tumor invasion.

In laboratory animals, they found that scatter factor greatly stimulates the formation of new blood vessels (angiogenesis), an essential step for tumor growth and spread (metastasis). They also found that invasive breast cancer tissue samples with higher levels of scatter factor have higher levels of von Willebrand factor (VWF), which is a protein produced by the lining of blood vessels. This suggests that higher levels of VWF may be associated with greater angiogenesis. In other experiments, the researchers found that levels of scatter factor were significantly higher in invasive breast cancer tissue than in benign breast lesions or noninvasive breast cancers (ductal carcinoma *in situ* [DCIS]). Invasive breast cancers had nearly four times the scatter factor content of DCIS tissue. Also, tumors that had spread to the axillary lymph nodes had higher levels of scatter factor than invasive cancers that had not yet spread beyond the breast,

although this difference was not as great as that seen between invasive breast cancers and DCIS tissue. Scatter factor levels did not vary by histologic (cell) type of invasive breast cancer. Dr. Rosen and his colleagues also demonstrated in an animal model that scatter factor can stimulate the growth of breast tumors. Human breast cancer cells, altered to produce high levels of scatter factor, were injected into mice. The researchers found that the mammary (breast) tumors grew much more rapidly in these mice than in mice receiving unaltered breast cancer cells.

Tissue specimens from the Long Island Jewish Frozen Tumor Bank at the Long Island Jewish Medical Center were used for the research. Since this LIBCSP-supported study, Dr. Rosen has continued his research on scatter factor, further advancing the understanding of its role in tumor development. The research was published in 1996.⁶¹

RDA Analysis of Breast Cancer

Michael H. Wigler, Ph.D., Cold Spring Harbor Laboratory, Cold Spring Harbor, New York

Dr. Wigler examined genetic changes in breast tumor tissue from patients on Long Island using a technique called representational difference analysis (RDA). In a pilot study, he demonstrated that the technique permits cloning of DNA probes that mark the presence of genetic lesions in tumors. Advances in the development of this technique as a research tool are of interest because certain point mutations in genes may be linked to environmental exposures and may be characteristic of specific environmental exposures. The research was published in 1995.⁶² The seed money provided through the LIBCSP for this pilot research was the foundation for a larger research effort subsequently funded by the DOD.

B. Intramural Research at NCI

New Statistical Methodology for Determining Cancer Clusters

Martin Kulldorff, Ph.D., University of Connecticut Health Center, Farmington, Connecticut
(Dr. Kulldorff was formerly with the NCI, Bethesda, Maryland.)

Dr. Kulldorff, while at NCI, and colleagues developed an innovative statistical technique that shows that women living in a broad stretch of the Northeastern United States, which includes Long Island, are slightly more likely to die from breast cancer than women in other parts of the Northeast. The study does not explain why these women are at higher risk of death, and the researchers note that the increase may be due to differences in well-established risk factors for breast cancer that they were unable to include in the analysis. The breast cancer mortality rate along a section of the East Coast stretching from New York City to Philadelphia was 7 percent higher than the rest of the Northeast. The study was descriptive and did not include an analysis of the risk factors. The research was published in 1997.⁶³

Geographic Influences on Women's Health

Susan R. Sturgeon, Dr.P.H., University of Massachusetts, Amherst, Massachusetts
(Dr. Sturgeon was formerly with the NCI, Bethesda, Maryland.)

Dr. Sturgeon has been conducting a study to determine if regional differences in the prevalence of established or suspected risk factors for breast cancer, and certain hypothesized environmental risk factors, may explain geographic variations in death rates for the disease. She began the research while at NCI. Findings from this study are expected to be published in 2004.

The study chiefly focuses on geographic variations among white women in the Northeast and South (where differences in breast cancer death rates are most pronounced), and on rural and urban variations in rates in these regions. It includes women from Nassau County, New York, as one of the densely populated areas. The Northeast area in the study includes Connecticut, Delaware, Maine, Maryland, Massachusetts, New Jersey, New Hampshire, New York, Pennsylvania, Rhode Island, Vermont, and the District of Columbia. The southern states are Alabama, Arkansas, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, and West Virginia. (Breast cancer death rates for black women do not differ as markedly by geographic area as for white women, and for this reason an analysis focusing on geographic variations would not be instructive.)

The research includes 3,800 white women, 25 years-of-age or older (selected by random-digit dialing). The women were interviewed by telephone for information about their age, menstrual and reproductive history, personal and family history of breast cancer, history of benign breast biopsies, exogenous estrogen use, body mass index, dietary fat intake, and alcohol consumption. Information also was obtained on the women's exposure to pesticides and other chemicals, automobile exhaust, sources of drinking water, and the proximity of their residences to landfills, airports, and factories.

The current study is a follow-up to a 1995 analysis by Dr. Sturgeon and colleagues of geographic differences in breast cancer death rates, which demonstrated that the mortality risk for breast cancer among white women is similar in the Northeast, Midwest, and West, after recognized risk factors for the disease are taken into account.³ Moreover, the differences between these regions and the South narrowed after accounting for such factors. The study did not explain all of the regional differences in breast cancer, but provided perspective and laid the groundwork for the current study.

New York State Cancer Registration Project

Brenda Edwards, Ph.D., NCI, Bethesda, Maryland

Dr. Edwards, Associate Director of the Surveillance Research Program, DCCPS, NCI, worked with the New York State Department of Health and Long Island cancer registrars to review state cancer registration and reporting procedures for breast cancer. She conducted a study of medical records of breast cancer cases on Long Island, and looked at the accuracy of reported stage of diagnosis for female residents using New York Cancer Registry data and a report from the U.S.

Centers for Disease Control and Prevention (CDC) on data from 1978 to 1982. The analysis indicated a high percentage (18 percent) of distant disease for Long Island. A 10 percent oversample was used to obtain 100 cases per year per county to reach a total of 600 cases. For 1989-1991 in Long Island, the stage distribution showed a smaller percentage of metastatic disease (7 percent) than in the older reported data (18 percent for 1978-1982). When comparing data reported to New York State to U.S. data, overall agreement was good (73 percent); however, misclassification was found at all stages and in both directions (upstaging and downstaging). The final, adjusted, stage distribution for 1989 and 1991 showed there was somewhat more regional disease in Long Island than was found in national data among white women.

IV. Geographic Information System for Breast Cancer Studies on Long Island

In 1999, NCI awarded a contract to AverStar, Inc., of Vienna, Virginia, to develop and implement the LI GIS. The contract was awarded for a base period of 2 years (Phase 1) and 3 option years (Phase 2). Phase 1 was for the development and delivery of the tool. Phase 2, which is now in progress, involves maintaining, expanding, and upgrading the system to respond to research needs. The total estimated cost for the system from FY 1999 through 2004 is \$5.8 million. Of this amount, CDC provided \$300,000 to support the LI GIS. (See Appendix H.)

The LI GIS is a dynamic research tool that provides a broad body of data in addition to statistical and GIS tools to facilitate research. Its primary intended use is as a tool for researchers to investigate relationships between breast cancer and the environment. It potentially could be used for research on other types of cancer and other diseases and conditions.

The LI GIS serves both the public and individual researchers. A mapping facility is under development that will provide the public a window into how the tool operates. The mapping facility, which will be part of the LI GIS public Web site, will give access to public databases and other information incorporated into the system that is not protected by privacy and other data restrictions, online maps, and software not subject to licensing restrictions. Development of the facility has been very challenging, chiefly because of software limitations that cause loading of the maps to take an unacceptable length of time. Some recent advances in software are anticipated to solve this problem. In the meantime, much descriptive information about the LI GIS currently is available on the Web site, and the tool itself is available for research use. The Web site is www.healthgis-li.com.

Researchers are invited to apply to use the LI GIS to study breast cancer and the environment on Long Island, as well as other types of cancer and other diseases and conditions. Access to the LI GIS, its data warehouse and software, and tools are obtained following an approval process.

The LI GIS contains:

- Data warehouse providing data from more than 80 datasets on demographic, environmental, and breast cancer incidence data on a geographic area, including Suffolk

and Nassau Counties in New York, plus a more limited set of data on other parts of New York near Long Island; metadata (data about source data that enables researchers to assess the usefulness and relevance of data for their purposes);

- Geographic mapping software and tools;
- Sophisticated statistical software and tools;
- Remote access to the tools and data warehouse;
- Access to the GIS Lab in Reston, Virginia;
- Data services; and
- Help Desk and online trouble reporting.

Researchers with approved projects may use the LI GIS data and software at no cost. There may be costs associated with providing data processing services for files and requests that are unusually complex. Funding is not provided for research, but NCI, NIEHS, and other NIH Institutes have investigator-initiated grant programs that can provide support for researchers' time and effort.

The five categories of data are:

- Geographic framework data, including road maps, water features, parks and landmarks;
- Demographic data, such as data on the age, race, sex, and income of the population;
- Health outcome and health care data, including breast cancer incidence and health facilities;
- Environmental data, including land use, land cover, railroads, traffic, water use, potential sources of water pollution; releases of chemicals into water, air, and soil; electrical power lines; radiation; and information on toxic chemicals and hazardous and municipal waste; and
- Other data, such as weather information and satellite image maps.

These data come from many sources. Sources of geographic data include the State Health Departments, Nassau and Suffolk Counties, and the U.S. Postal Service. Sources for demographic data include the U.S. Bureau of the Census. Health data sources include the State Health Departments and the CDC. Environmental data are provided by the State Health Departments, U.S. EPA, USGS, and U.S. Department of Agriculture (USDA). Information about each data source is publicly available on the LI GIS Web site in the Metadata Browser section.

Implementation of the LI GIS is guided by a 17-member Oversight Committee that oversees development of the system, reviews data to be included in it, and offers advice on strategies for protecting the confidentiality of data. The committee has broad representation from federal, state, and local government, academia, and the community. It includes experts in environmental epidemiology and exposure assessment, environmental sciences, geography, spatial statistics, bioethics, radiation, and community members.

Soon after the contract for the LI GIS was awarded, in 1999, NCI hosted a series of town meetings on Long Island to provide information on development of the research tool and to invite the public to contribute information on environmental exposures that may not be in existing databases. (See Appendix I.) Community members may continue to provide information. The information is available to researchers using the LI GIS. In 2000, NCI returned to Long Island to provide the community a preview of the system. (See Appendix J.) See *Community Outreach/Relations* section for further information.

The availability of the LI GIS has been widely publicized at scientific meetings through presentations, exhibits, and flyers. Interest thus far has been limited, and no research proposals have been submitted, although a few investigators have expressed serious interest, and scientists appear enthusiastic about its potential. This is believed to be largely because the use of GIS technology in cancer research is new, and few cancer epidemiologists are using GISs in conjunction with their research. The LI GIS team continues to pursue avenues to attract potential users.

V. Relevant Non-LIBCSP Research

During the 1990s, NCI and NIEHS funded the Northeast Mid-Atlantic (NEMA) Breast Cancer Study to investigate organochlorine compounds and PCBs as possible causes of risk for breast cancer in the Northeast and Mid-Atlantic regions of the country. Five studies were conducted, after which the investigators combined their data for analysis. In the individual studies and the pooled analysis, the researchers found that exposure to organochlorine compounds and PCBs did not appear to explain the elevated rates for breast cancer in the Northeast and Mid-Atlantic regions.⁶⁴ The women in the five studies totaled 1,400 breast cancer patients and 1,642 controls. Two of the studies were conducted among women in New York State, one was in Connecticut, and one was in Maryland. One-half of the women in the fifth study, the nationwide Nurses' Health Study, live in the northeastern states, including Maryland. In each of the studies, blood was drawn from patients and controls and tested for DDE, the major breakdown product of DDT, and for PCBs. The researchers used a standardized approach to data analysis across all five studies and did not find a consistent association in the various subgroups: Caucasian women, African-American women, women of various body mass and lactation histories. (The NEMA Study was conducted in response to a request of the 1992 Senate Appropriations Committee to study factors that may contribute to the elevated rates of breast cancer in the Northeast and Mid-Atlantic regions of the country. A report was submitted to Congress in 2000.)

Long Island community members expressed interest in having a separate case-control study conducted on African-American women and breast cancer. The African-American population of Nassau and Suffolk Counties was too small for such a study. African-American women were included in the LIBCSP case-control studies, although separate analyses were not possible because of small numbers. Dr. Gammon increased African-American participation in her study by analyzing all of the blood samples from this population in her analysis published in 2002. In addition, all study participants who identified themselves as African American or black and who met the residency requirement were invited to participate in the home study.

Other research opportunities enable researchers to focus on breast cancer risk among African Americans. Examples are the Carolina Breast Cancer Study (CBCS), which includes a large African-American population in 24 counties of North Carolina. In 2000, researchers reported finding no overall association between plasma levels of DDE, and total PCBs, and increased risk for breast cancer among African-American and white women. There was an association between total PCBs and risk for breast cancer among women who had a high body mass index (BMI), however, which suggests the need for further study.⁶⁵ Other analysis on the overall CBCS population indicated that increased duration of farming may be inversely associated with risk for breast cancer. The findings, however, suggested that risk may be increased for a small subset of women with probable high exposures to pesticides or who reported not wearing protective clothing or gloves while applying pesticides.⁶⁶ The CBCS was funded by NCI, and the analyses on DDE and PCBs were funded by NCI and NIEHS, with David Savitz, Ph.D., of UNC at Chapel Hill as the Principal Investigator.

With respect to EMFs, findings by CBCS researchers found little evidence to support the possibility of an association between EMF exposures in the occupation setting and increased risk for breast cancer.⁶⁷ Furthermore, another research group conducted a nested, case-control study of residential exposure to EMFs and risk for breast cancer with a cohort of African Americans, Latinas, and Caucasians in Los Angeles County, California. They did not find an association between residential exposures to EMFs and increased risk for breast cancer in the three groups. This research was conducted by NIEHS and researchers at the University of Southern California, Los Angeles; University of Hawaii, Honolulu; and EM Factors, Richland, Washington.⁶⁸ Funding was provided by NIEHS, NCI, DOD, and the California Department of Health Services. A cohort of African-American women is being followed to investigate the effects of a variety of potential risk factors on the incidence of breast cancer, other cancers, and other serious illnesses. These risk factors include obesity, physical activity, alcohol consumption, diet, oral contraceptive use, and postmenopausal female hormone use. The Black Women's Cohort: A Follow-Up Study for Causes of Illness in Black Women is being conducted by Lynn Rosenberg, Sc.D., of Boston University, Boston, Massachusetts, and is funded by NCI.

NCI-funded researchers currently are recruiting 100,000 residents age 40-79, both sexes, of whom more than two-thirds are to be African American, from the southeastern United States, to establish a long-term prospective cohort to study risk factors for breast and other cancers. The Southern Community Cohort Study is being conducted by William Blot, Ph.D., Vanderbilt University, Nashville, Tennessee, and International Epidemiology Institute, Ltd., Rockville, Maryland.

VI. Community Outreach/Relations

NCI, NIEHS, and the LIBCSP investigators have undertaken many different types of activities to keep concerned members of the community, governmental entities, medical and research institutions, and private organizations informed about the LIBCSP and involved in its activities.

NCI and NIEHS staff have traveled to Long Island on numerous occasions to give presentations and meet with groups. Periodic “Updates” and “Questions and Answers” were issued. (See Appendix K.) Also, a Web site provides extensive information about the Project, and a separate, but linked, Web site is available about the LI GIS (LIBCSP Web site: epi.grants.cancer.gov/LIBCSP; LI GIS Web site: www.healthgis-li.com).

A variety of public programs have been hosted. In 1995, a town meeting was held to discuss breast cancer on Long Island and to report on the start of the LIBCSP studies. Meetings of the *ad hoc* Advisory Committee to the LIBCSP, which were open to the public and took place in the Long Island/New York area, were held in 1995, 1996, and 1997. Typically, about 100 community members and scientists attended. For the LI GIS, three workshops were held for the community and one workshop was held for LIBCSP investigators in 1996 to obtain their input on the development of the RFP to develop the research tool. Following the award of the contract for the LI GIS, in the fall of 1999, seven town meetings were hosted in four locations on Long Island to obtain information from residents about sources of environmental pollution that may not be in existing records. Members of the Long Island Breast Cancer Network (LIBCN), a coalition of Long Island breast cancer groups, helped to plan the publicity and sites for the town meetings and to promote them. Individuals may continue to contribute via the LI GIS Web site. In 2000, the LI GIS team hosted a preview of the system on Long Island, and invited the community to a meeting of the Oversight Committee.

NCI staff, as well as some of the scientists who conducted the LIBCSP studies, regularly reported on the Project at meetings of the LIBCN through 2002. The NCI/NIEHS Project team continues to keep the LIBCN informed and occasionally attends the meetings. The *ad hoc* Advisory Committee to the LIBCSP included five community members (Ms. Francine Kritchek, Ms. Dee McCabe, Ms. Karen Miller, Ms. Carolyn Thompson Taylor, and Ms. Victoria White). The community representatives established an investigator liaison program in which a community member was assigned to each of the LIBCSP studies to follow their progress.

The Oversight Committee for the LI GIS includes five community members (Ms. Barbara Balaban, Ms. Karen Miller, Ms. Sarah Meyland, Ms. Martha Rogers, and Ms. Victoria White). This committee has met periodically in person and via telephone conference since its formation in 2000, and continues to do so. The community representatives also have helped in development of the public mapping facility.

Dr. Gammon and other members of the Breast Cancer and the Environment on Long Island investigative team made many detailed presentations to community and health professional

groups to publicize the opportunity for eligible Long Island women to participate in the case-control study, as well as to give progress reports. The research team maintained a dedicated telephone line for inquiries, periodically published a newsletter for study participants, and had a Web site during the study's recruitment and field work phases. (See Appendix L.) The external advisory committee for the study included a Long Island community member who also is a member of the present Data Sharing Committee (Ms. Barbara Balaban). Dr. Gammon also sought the advice and assistance of members of the LIBCN in outreach efforts. Breast cancer advocates provided funds for Dr. Gammon to include in the analysis data on Long Island women who were diagnosed with DCIS.

When the major findings from Dr. Gammon's study were to be published in 2002, she gave a detailed briefing to members of the LIBCN and hosted a press conference on Long Island. She obtained permission from the journal for the pre-embargo briefing for the LIBCN. LIBCN members arranged for the meeting space for the briefing and press conference. NCI's Dr. Winn and Ms. Anderson attended the events. Dr. Gammon continues to keep community members informed of additional analyses underway, and on the follow-up study on women with breast cancer who participated in the initial study.

Dr. Leske formed a community advisory group to provide a liaison between the EMFs and Breast Cancer on Long Island Study and the community. The advisors met regularly with the research team and contributed to the study's educational and community aspects (Ms. Mary Dowden, Ms. Miriam Goodman, and Ms. Mary Joan Shea). They also secured funds from breast cancer advocacy groups to enable the researchers to purchase additional EMF meters to expedite their work. When the major findings from the study were published in 2002, Dr. Leske hosted detailed briefings for the community advisory group and community members, and a press conference. Dr. Winn and Ms. Anderson attended. Dr. Leske continues to keep the community advisory group and community members informed of the outcome of additional analyses.

The Metropolitan New York Registry for families with a history of breast or ovarian cancer has a special toll-free number that area residents may call to inquire about enrolling in the Registry (1-888-METRO-08). In addition to Columbia University, where the registry is based, there was a location at Stony Brook University from 1997 through 2000, where Long Island residents could go to learn about the Registry and enroll. Dr. Senie and her team have given many presentations to publicize the opportunity for eligible families to enroll. The Registry also publishes a newsletter and has a Web site (www.metronyregistry.org). A consumer representative serves on its advisory group.

Community members submitted a list of chemicals of interest to them as possible breast carcinogens. EPA, NIEHS, and IARC provided information from their various databases on carcinogenicity and toxicology to help assemble summary information about the chemicals. Ruth Allen, Ph.D., of the U.S. EPA, while on a detail to NCI and on a continuing basis after she returned to her agency, led the effort to develop the summary tables. (See Appendix M.) U.S. EPA's Richard Hill, M.D., Ph.D., Science Advisor, Office of Prevention, Pesticides, and Toxic Substances, facilitated acquisition of the various databases. Reviews of the list of chemicals

indicated that the majority of them were or are being tested in the LIBCSP, either in drinking water, soil, dust, or in blood samples. Dr. Allen coordinated one review, made copies available of the summary tables on computer disk to community members, and periodically met with them to explain the work. Dr. Gammon also conducted a review and discussed it with community members. A member of the LIBCN served as the liaison with interested community members (Ms. Elsa Ford).

VII. Future Directions

Findings on the primary hypotheses of the initial LIBCSP studies have been published, but researchers continue to analyze data from the Breast Cancer and the Environment on Long Island Study and the EMFs and Breast Cancer on Long Island Study. Also, women with breast cancer who participated in the Breast Cancer and the Environment Study continue to be followed.

Described below are some of the other investigations and activities underway that are further exploring possible environmental causes of breast cancer.

Breast Cancer and the Environment Research Centers

In 2001 and 2002, NIEHS sponsored a series of workshops and meetings to discuss how best to pursue further study on breast cancer and the environment. These meetings were attended by scientists, representatives from breast cancer advocacy groups, and health care practitioners. Based on the discussions, NIEHS and NCI partnered in a Request for Applications (RFA) inviting proposals to create a network of research centers in which multidisciplinary teams of scientists, clinicians, and breast cancer advocates work collaboratively on a unique set of scientific questions that focus on how chemical, physical, biological, and social factors in the environment work together with genetic factors to cause breast cancer.

In September 2003, NIEHS, in collaboration with NCI, funded four new Breast Cancer and the Environment Research Centers (BCERC) to study the prenatal-to-adult environmental exposures that may predispose a woman to breast cancer. A total of \$5 million a year over 7 years, or \$35 million, is being provided in funding. (See Appendix N.)

The centers and their principal investigators are: University of Cincinnati, Cincinnati, Ohio, Sue C. Heffelfinger, M.D.; Fox Chase Cancer Center, Philadelphia, Pennsylvania, Jose Russo, M.D.; University of California at San Francisco, Robert A. Hiatt, M.D., Ph.D.; and Michigan State University, East Lansing, Michigan, Sandra Z. Haslam, Ph.D.

The centers will work collaboratively on two main fronts. Using animals, they will study the development of mammary tissue and the effects of specific environmental agents. In the second collaborative project, they will enroll different ethnic groups of young girls and study their life exposures to a wide variety of environmental, nutritional, and social factors that impact puberty. Early puberty has been shown to increase breast cancer risk later in life. The four centers will interact as a single program, although with some specialization at each center. All the centers

will work with advocacy groups to add their insight and experience to the research effort. Breast cancer survivors and members of advocacy groups are an integral part of each center's study team and also are represented on the National Advisory Environmental Health Sciences Council Working Group on Breast Cancer and the Environment that oversees the projects.

Sister Study

Scientists at NIEHS are conducting a prospective study of a cohort of unaffected sisters of women who have had breast cancer. Recruitment to the study began in the fall of 2002. The Sister Study will prospectively examine environmental and familial risk factors for breast cancer and other diseases in a cohort of 50,000 sisters of women who have had breast cancer. Such sisters have about twice the risk of developing breast cancer as other women. The frequency of any relevant genes and shared risk factors also will be higher, thus enhancing the statistical power of the study to detect risks. Sisters are expected to be highly motivated, and response rates and compliance over time are expected to be high. Thus, studying sisters will enhance researchers' ability to understand the interplay of genes and environment in breast cancer risk and to identify potentially preventable risk factors. The prospective design will allow the researchers to assess exposures before the onset of disease, thus avoiding biases common to retrospective studies and aiding in causal interpretation. The study also will create a framework from which to test new hypotheses as they emerge. The Principal Investigator is Dale Sandler, Ph.D., Acting Chief, Epidemiology Branch, Environmental Diseases and Medicine Program, Division of Intramural Research, NIEHS.

Cohort Consortium

With recent discoveries in genetics, it has become increasingly clear that elements in the environment or a person's lifestyle can damage genes, and that individuals differ in their susceptibility to disease. To make progress, new ways need to be developed to study cancer susceptibility, environmental exposures, and their interactions. Large-scale collaborations in the genetic and molecular epidemiology of cancer will be needed.

With this in mind, in 2003, NCI launched a new initiative to pool data and biospecimens from 10 large study populations to conduct research on gene-environment interactions in cancer etiology. The investigative teams will collaborate on studies of hormone-related gene variants and environmental factors involved in the development of breast and prostate cancer. For the breast cancer research, data will be drawn from 6,160 patients with the disease. By pooling data and samples, it is believed that epidemiologists and genomicists more easily can generate the large numbers of study participants that are essential to conduct population studies into the role of genes and the environment. An important aim of this initiative is to prove the principle that pooling data and biospecimens across large-scale studies through consortia arrangements is an effective way to approach research on genes and the environment, and their interactions.

Metropolitan New York Registry

The Metropolitan New York Registry for families with a history of breast or ovarian cancer continues to be funded to provide data and biospecimens for research. One pilot study using biospecimens from women participating in the Registry is expanding upon the LIBCSP research conducted by Dr. Bradlow and Dr. Kabat on estrogen metabolites in urine as biomarkers for risk for breast cancer (see *Research and Findings* section). This study is investigating whether the ratio of 2-hydroxyestrone/16 α -hydroxyestrone is lower in families with a stronger inherited pattern of breast cancer risk as compared to families with a weaker pattern, and in paired sisters who differ by their breast cancer status. This study is funded by NCI through the Registry. Dr. Ahsan, of Columbia University, New York, is analyzing the data.

Regional Variations in Breast Cancer Risk

In response to an RFA in 1999, NCI and NIEHS funded five investigations to explore reasons for regional variations in breast cancer rates in the United States. The research projects are ongoing:

- A study is examining SEER-Medicare linked data to examine variation in breast cancer incidence, survival, and mortality by health service area within NCI's Surveillance, Epidemiology, and End Results (SEER) Program sites. SEER is the most authoritative source of information on cancer incidence and survival in the United States. Its data are collected from registries that cover the populations of Connecticut, Iowa, New Mexico, Utah, and Hawaii; the metropolitan areas of Atlanta, Detroit, Georgia, San Francisco-Oakland and San Jose-Monterey, Los Angeles County, Seattle-Puget Sound.) James Goodwin, M.D., the University of Texas Medical Branch, Galveston, Texas, is the Principal Investigator.
- A population-based study is investigating established and potential risk factors that may be responsible for longstanding regional variations in breast cancer rates within Wisconsin. Environmental exposures such as PCBs, DDT, and other xeno-estrogens (substances foreign to the body that act like estrogen hormones) are included. Breast cancer incidence, mortality, and survival rates within the state are to be studied. Patrick Remington, M.D., M.P.H., University of Wisconsin Comprehensive Cancer Center, Madison, Wisconsin, is the Principal Investigator.
- Factors that may be responsible for regional differences in breast cancer incidence rates within California are being studied. This research project includes use of a GIS and grouped data sources to evaluate the potential influences of sociodemographic factors, environmental agents, and established risk factors. A substudy is exploring urban/rural variations in biomarkers of PAHs and phytoestrogens. Peggy Reynolds, Ph.D., of the California Department of Health Services, Emeryville, California, is the Principal Investigator.

- Regional variations in breast cancer incidence rates within Massachusetts are being studied to determine if the differences are random (due to chance) or if there are causal factors that may be identified. Joseph Sheehan, Ph.D., of University of Connecticut Health Center, Farmington, Connecticut, is the Principal Investigator.
- A case-control study is being conducted in Connecticut to examine the association between genetic variability in three major *GST* genes (*GSTM1*, *GSTT1* and *GSTP1*) and increased risk for breast cancer, and to determine if these genes modify the association between environmental factors and risk for the cancer. Tongzhang Zheng, M.D., Sc.D., of Yale University, is the Principal Investigator.

Exposure Assessment Methods

Much remains to be learned to achieve scientifically credible and realistic assessments of environmental exposure and health risks. In response to an RFA in 2001, NCI and NIEHS funded 11 studies to further development of research tools and improved methods for assessing environmental exposures that are potentially applicable for cancer research, including breast cancer.

Geographic Information Systems

In the area of GIS development, NCI issued a Program Announcement (PA) in 2000 to encourage investigators to submit proposals for studies to refine GIS and related methodologies and use the technology for cancer research. A total of 12 grants were awarded in 2001 and 2002.

Transagency Task Force

A transagency task force initiated by NCI is making steady progress on a proposed plan to address breast cancer rates in Marin County, California, and other counties in the United States. NCI convened a meeting in 2003 with representatives from NIEHS, CDC, and the U.S. EPA to develop guiding principles for addressing high cancer incidences throughout the country, including Marin County. This is one in a series of planned meetings focused on a science-based approach for assessing the contribution of environmental exposure to breast cancer risk. The task force is assessing current research efforts and available technologies and processes, which may be valuable in answering questions about the impact of the environment on breast cancer risk and discussing how better approaches might be developed.

Data from the 2000 census have enabled NCI researchers to recalculate breast cancer rates for Marin County, which indicated that rates are substantially lower than those calculated using 1990 census information. This discrepancy between using the 1990 and 2000 census data is due to projected population growth differing considerably from actual population growth. Comparisons of recalculated rates to other parts of California and the country are in progress.

With NCI's encouragement, the Northern California Cancer Center in Union City, California, submitted a research application for funding to examine the prevalence of established breast cancer risk factors. In September 2003, the proposal was funded via NCI's Rapid Response Surveillance Studies (RRSS) mechanism, which allows researchers to conduct innovative population-based surveillance and outcome studies on scientific inquiries deemed to be of high priority to NCI, Congress, and advocacy groups.

Also in September 2003, via NCI's RRSS mechanism, investigators at the Northern California Cancer Center were funded to develop statistical models to predict attributable risk (the amount of disease that could be due to specific risk factors) based on three modifiable breast cancer risk factors: alcohol use, hormone replacement therapy, and breastfeeding. The results of this analysis can be used to measure the benefits of interventions that were designed to modify these risk factors.

VIII. Conclusion

The mandate of the Public Law has been met with the successful conduct of the epidemiologic studies and the development of the LI GIS. The LIBCSP applied the best available science and technologies in pursuit of relationships between the environment and increased risk for breast cancer, and yielded high-quality research. LIBCSP's accomplishments include:

- Demonstrated that organochlorine compounds (e.g., pesticides including DDT/DDE, dieldren, and chlordane, and PCBs) are not associated with increased risk for breast cancer on Long Island;
- Found that PAHs were associated with a modest increased risk for breast cancer, which will need to be confirmed in studies of other populations;
- Found that PCBs may be associated with an increased risk for recurrence of breast cancer, which is being investigated further (numbers were small and no association had been seen with initial diagnosis of cancer);
- Demonstrated that EMFs are not associated with increased risk for breast cancer on Long Island;
- Confirmed the presence of established risk factors for breast cancer among women on Long Island;
- Supported exploratory research on urinary biomarkers for early detection of breast cancer;
- Demonstrated effective methods to improve breast cancer screening among underusers of mammography;

- Furthered laboratory research on mechanisms of action and susceptibility to breast cancer that have contributed to our understanding of the process of tumor development;
- Developed new and improved research methods to advance epidemiologic investigations;
- Established a breast/ovarian cancer family registry that is a research resource for investigators, provides opportunities for families to participate in research, and now is part of a larger NCI program;
- Developed the LI GIS as a research tool for studying relationships between the environment and breast cancer;
- Funded pilot studies on the use of LI GIS in research on breast cancer and the environment;
- Provided the basis for spinoff studies using data and biospecimens from the centerpiece case-control study for investigations on genetic susceptibility and the potential role of gene-environment interactions in breast cancer causation. These studies are conducted independent of the LIBCSP with support from various research funding organizations; and

A new generation of research on breast cancer and the environment is underway. Although research may not be ongoing in a given geographic location, the overarching aim of epidemiologic research is to generate findings that can be generalized to the larger population. NCI and NIEHS remain committed to advancing our understanding of potential relationships between environmental exposures and risk for breast cancer.

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